Exhibit A

CYTOGEN

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Study Demonstrates that Overexpression of Prostate-Specific Membrane Antigen Correlates with Disease Recurrence in Primary Prostate Cancer and Independently Predicts Disease Outcome

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Despite current interest in Prostate-Specific Membrane Antigen (PSMA) as a target of therapy for patients with hormone-refractory prostate cancer and clinical use of PSMA-directed tumor imaging with Cytogen's ProstaScint®, PSMA expression in primary prostate cancer has not been evaluated previously as a stand-alone prognostic marker.

Princeton, N.J., (January 5, 2004) – Cytogen Corporation (Nasdaq: CYTO), a product-driven, oncology-focused biopharmaceutical company, today announced the publication of clinical data showing that overexpression of Prostate-Specific Membrane Antigen (PSMA) in primary prostate cancer correlates with other adverse traditional prognostic factors and independently predicts disease recurrence. Overexpression of PSMA was determined by immunohistochemical staining using the same monoclonal antibody (7E11) utilized in Cytogen's ProstaScint® molecular imaging agent. The data was recently reported in the medical journal *Clinical Cancer Research* (Volume 9, No. 17, pp. 6357-6362).

Cytogen's ProstaScint molecular imaging agent is the first and only commercial product targeting PSMA, a transmembrane protein that is expressed on prostate cancer cells at all stages of disease, including advanced or metastatic disease. ProstaScint consists of a murine monoclonal antibody (7E11) directed against PSMA that is linked to the radioisotope Indium-111. A radioisotope is an element, which, because of nuclear instability, undergoes radioactive decay and emits radiation. Due to the selective expression of PSMA by prostate cancer cells, the ProstaScint molecular imaging procedure can detect the extent and spread of prostate cancer using a standard gamma camera.

"We believe that the publication of clinical data showing that overexpression of PSMA in primary prostate cancer correlates with other adverse traditional prognostic factors and independently predicts disease recurrence as determined using the 7E11 monoclonal antibody further validates our belief that ProstaScint, in conjunction with other diagnostic information, is an important and clinically-useful molecular imaging procedure," said Michael D. Becker, President and Chief Executive Officer of Cytogen Corporation. "While many nuclear medicine physicians experienced in the use of ProstaScint believe that the agent identifies the spread and location of prostate cancer, there has been some uncertainty given the inherent limitations of obtaining histopathologic correlation in these patients. However, the recent presentation of data from a large, retrospective outcomes study at the Radiological Society of North America (RSNA) annual meeting showing that uptake with ProstaScint is associated with a poor prognosis, combined with this new study showing that

overexpression of PSMA correlates with disease recurrence and independently predicts disease outcome in primary prostate cancer, provides additional support to the belief that ProstaScint imaging can indeed identify metastatic disease."

Using prostatectomy specimens, immunohistochemical staining for PSMA using the same murine monoclonal antibody utilized in ProstaScint (the 7E11 antibody) was performed on formalin-fixed paraffin-embedded sections of 136 cases of prostate cancer. Cytoplasmic immunoreactivity was scored for intensity and distribution, and results were correlated with tumor grade, pathological stage, DNA ploidy status (Feulgen spectroscopy), and disease recurrence. PSMA mRNA expression in selected primary tumors and metastatic lesions was also detected using in situ hybridization and autoradiography.

Generally, prostate cancer cells expressed relatively increased levels of PSMA as compared with benign elements. Among the prostate cancer cases, increased (high) PSMA expression correlated with tumor grade (P = 0.030), pathological stage (P = 0.029), aneuploidy (P = 0.010), and biochemical recurrence (P = 0.001). The mean serum prostate-specific antigen (PSA) level of 18.28 ng/ml at the time of diagnosis for the PSMA-overexpressing tumors was significantly greater than the mean serum PSA of 9.10 ng/ml for the non-PMSA-overexpressing group (P = 0.006).

On multivariate analysis, pathological stage (P = 0.018) and PSMA expression (P = 0.002) were independent predictors of biochemical recurrence. PSMA protein overexpression in high-grade primary prostate cancer tumors and metastatic lesions also correlated with increased PSMA mRNA expression levels using in situ hybridization and autoradiography. Kaplan-Meier survival curves for PSMA expression in prostate cancer patients showed that patients with tumors with high PSMA expression suffered a significantly increased rate of recurrent disease (P = 0.001) as compared with those whose tumors featured a relatively lower PSMA expression.

NOTE:

ProstaScint is indicated as a diagnostic imaging agent in newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation and who are thought to be at high risk for pelvic lymph node metastases. ProstaScint is also indicated in post-prostatectomy patients and a negative or equivocal standard metastatic evaluation in whom there is a high clinical suspicion of occult metastatic disease.

A copy of the full prescribing information for ProstaScint may be obtained in the United States from Cytogen Corporation by calling toll free 800-833-3533 or by visiting the Company's web site at http://www.cytogen.com.

About Cytogen Corporation

Cytogen Corporation of Princeton, NJ is a product-driven, oncology-focused biopharmaceutical company. Cytogen markets proprietary and licensed oncology products through its in-house specialty sales force: Quadramet® (a skeletal targeting therapeutic radiopharmaceutical for the relief of pain due to bone metastases); ProstaScint® (a monoclonal antibody-based imaging agent used to image the extent and spread of prostate cancer); and NMP22® BladderChek™ (a point-of-care, *in vitro*

diagnostic test for bladder cancer). Cytogen has exclusive U.S. marketing rights to Combidex®, an ultrasmall superparamagnetic iron oxide contrast agent for magnetic resonance imaging of lymph nodes that is pending clearance by the U.S. Food and Drug Administration. Cytogen's pipeline comprises product candidates at various stages of clinical development, including fully human monoclonal antibodies and cancer vaccines based on PSMA (prostate specific membrane antigen) technology, which was exclusively licensed from Memorial Sloan-Kettering Cancer Center. Cytogen also conducts research in cellular signaling through its AxCell Biosciences research division in Newtown, PA. For more information, please visit the Company's website at www.cytogen.com, which is not part of this press release.

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**Human
PATHOLOGY**

Original contribution

Prostate-specific membrane antigen expression as a predictor of prostate cancer progression☆

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Summary Distinguishing aggressive prostate cancer from indolent disease represents an important clinical challenge, because current therapy may lead to overtreatment of men with limited disease. The prostate-specific membrane antigen (PSMA) is a membrane-bound glycoprotein that is highly restricted to the prostate. Previously, studies analyzing the expression of PSMA have found an up-regulation in correlation with prostate cancer, particularly in advanced cancer. This association is ideal for an application as a prognostic marker. In the current study, we characterized PSMA expression in a high-risk cohort and evaluated its potential use as predictive marker of prostate-specific antigen (PSA) recurrence. PSMA expression was analyzed by immunohistochemistry using tissue microarrays composed of tumor samples from 450 patients. Protein intensity was recorded using a semiautomated quantitative microscope system (ACIS II; Clarient Chromavision Medical Systems, San Juan Capistrano, CA). PSMA expression levels differed significantly ($P < .001$) between benign prostatic tissue, localized prostate cancer, and lymph node metastases. Dividing the cohort into high- and low-PSMA expressing cancers based on the median area of positive staining, we found that high PSMA levels were associated with significant increase of PSA recurrence ($P = .004$). This was independent of clinical parameters such as lymph node tumor burden (lymph node density, >20%; $P < .001$), extraprostatic extension ($P = .017$), seminal vesicle invasion ($P < .001$), and high Gleason score (8-10, $P = .006$). In a multivariate model, PSMA expression and metastases to pelvic lymph nodes were significantly associated with time to PSA recurrence (HR, 1.4; 95% confidence interval,

1. Introduction

A randomized clinical trial comparing watchful waiting with radical prostatectomy demonstrated significant risk reduction in the development of metastatic disease and cancer-specific death in clinically localized prostate cancer. However, this study also suggests that 19 men require surgical treatment to prevent one clinical event [1]. Therefore, molecular biomarker discovery needs to focus on distinguishing aggressive prostate cancer requiring treatment from indolent disease that may be expectantly followed with the option of delayed treatment if needed. Distinct sets of genes and proteins have been identified to be associated with the progression from precursor lesions to localized disease and eventual hormone refractory metastatic disease [2]. Prostate-specific membrane antigen (PSMA) is a type II transmembrane glycoprotein [3], which is negatively regulated by androgen. PSMA is significantly overexpressed in androgen-independent prostate cancer [4]. Increased PSMA expression in prostate cancer is associated with higher tumor grade [5,6] and a high risk of disease progression as defined by biochemical recurrence after radical prostatectomy [7].

Introduction of a more widespread prostate-specific antigen (PSA) screening has led to a dramatic increase in the identification of early localized prostate cancer. In areas of the world with less rigorous screening approaches, high-stage and metastatic prostate cancer represents a higher percentage of new cancer cases [8]. In a high-risk cohort with incomplete PSA screening, we analyzed PSMA expression to determine a potential clinical utility in the setting of high-risk prostate cancer treatment.

2. Materials and methods

2.1. Patient population and tissue collection

This study included 450 patients with prostate cancer diagnosed at the University of Ulm Hospital, Ulm, Germany, between the years 1986 and 2000. For these men, we compared PSMA expression in different histopathologic categories (including 24 benign, 225 localized prostate cancer, 73 hormone-naïve lymph node metastases, and 128 hormone refractory distant metastases of different organ sites) [8,9]. Among these, 93 men (63.4 years, 50.4-76.1 years [mean age, range]) who had localized and locally advanced prostate cancer underwent radical prostatectomy and pelvic lymph node dissection with curative intent but did not receive neoadjuvant (preoperative)

androgen ablation therapy or receive androgen ablation therapy before PSA recurrence occurred; we further examined the association between PSMA expression and time to PSA recurrence.

The study protocol was approved by the Internal Review Board. This cohort was recently described [8]. All prostatic adenocarcinomas were graded according to the system originally described by Gleason [10,11]. Staging and grading was centrally performed by a genitourinary pathologist (M. A. Rubin) based on American Joint Committee on Cancer guidelines.

Metastatic density of removed lymph nodes was assessed on hematoxylin and eosin slides stratifying them into 2 groups: volume of lymph node metastases less than 20%, where less than 20% of the total lymph node mass was occupied by metastases; and volume of lymph node metastases greater than 20%, where more than 20% of the total lymph node mass was occupied by metastases.

For all cases, the Hybritech platform (BeckmanCoulter, Fullerton, CA) was used for serum PSA level measurement before surgery (28.2 ng/mL, 1-248 ng/mL [mean, range]), then every 6 months after the surgery during the first 2 years, and at least yearly afterward (mean [maximum] follow-up: 2.8 [7.7] years). PSA failure was defined as serum PSA level greater than 0.4 ng/mL during follow-up, and the earlier date of 2 consecutive increments was defined as date of failure.

On average, 4 tissue microarray (TMA) cores for sample were available to evaluate. A minimum of 3 cores per sample is what we have previously considered optimal for outcome studies [12].

2.2. Immunohistochemistry

Sections of 4-μm-thick paraffin-embedded TMAs were dewaxed and rehydrated with xylene and ethanol. After immersion in 10 mmol/L citrate buffer (pH 6.0), the slides underwent pressure cooking pretreatment for 10 minutes for

Table 1 PSMA expression profile of different histopathologic categories (n = 450)

Histopathologic category	Mean z intensity (SD) (mean, −0.64)	No. of cases
Benign	−0.58 (0.6)	24
PCa	−0.05 (0.9)	225
LN Mets	0.60 (0.7)	73
HR Mets	0.01 (0.9)	128

LN Mets indicates lymph node metastases; HR Mets, hormone refractory metastases.
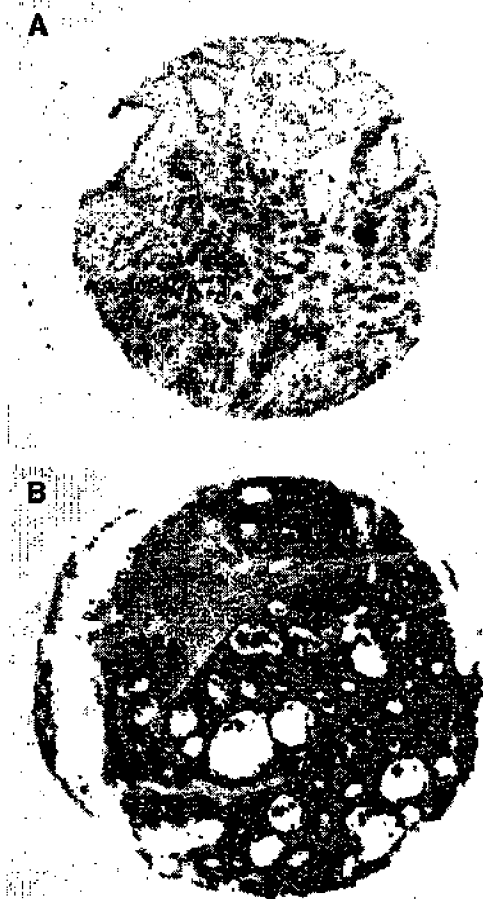
Fig. 1 PSMA immunoreactivity in epithelial cell membrane and/ or cytoplasm. A, Benign epithelium (upper third of core) with almost no staining of the secretory cell layer, overall corresponding to low PSMA expression, and localized prostatic adenocarcinoma (lower two thirds of core) with high PSMA expression in virtually every neoplastic cell. B, Lymph node metastasis of prostatic adenocarcinoma with very high staining intensity for PSMA in all cancer cells. A and B, Immunoperoxidase stains with hematoxylin counter stain.
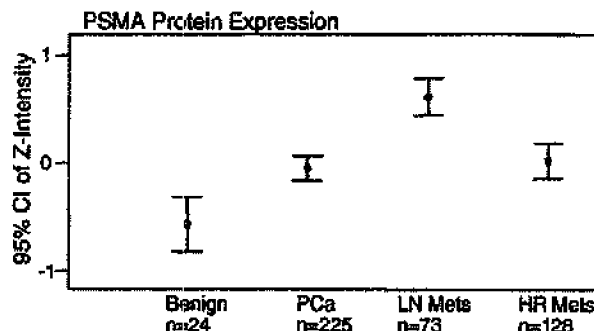

Fig. 2 Error bar chart of mean PSMA expression of different histopathologic categories: benign prostatic epithelium (Benign), localized PCa, hormone-naïve regional lymph node metastases (LN Mets), and hormone refractory metastases at different sites (HR Mets). Differences between histopathologic categories are significant ($P < .001$), except for PCa versus HR Mets.

optimal antigen retrieval. The primary antibody, a mouse antihuman PSMA monoclonal antibody (3E6; DAKO, Carpinteria, CA) of the IgG1 isotype directed against the internal domain of the PSMA protein, was incubated in a 1:200 dilution. The secondary antibody was biotin labeled and was applied for 30 minutes. Labeled streptavidin-biotin amplification method (DAKO K0679) was carried out for 30 minutes followed by peroxidase/diaminobenzidine substrate/Chromagen. The slides were counterstained with hematoxylin. The brown DAB area of immunohistochemical cytoplasmic and/or membranous staining was determined for each core and scored based on color threshold settings using a semiautomated quantitative image analysis system (ACIS II; Clarient Chromavision Medical Systems, San Juan Capistrano, CA) that has been previously

validated. The ACIS II image analysis system is a very time efficient and objective way in evaluating potential biomarker [13]. The output data of PSMA expression are represented by a continuous scale of DAB brown area and average DAB staining intensity for each core, ranging from 0 to 255. The PSMA expression intensity of each array was normalized by calculating the z score for each core. The z score normalization functions to equalize the immunohistochemical experiments on different TMAs due to variability of staining. The converted z scores were then aggregated into one large data set. Tissue cores of some patients were represented on more than one TMA, and after combining all z values for each patient, we determined the mean z score intensity of DAB staining for each patient.

2.3. Statistical analysis

The differential PSMA expression in the histopathologic categories was assessed using t test. To examine the association between PSMA expression and the time to PSA recurrence, we used Cox proportional hazards regression model for univariate and multivariable analyses of continuous and categorical data of clinical and pathology para-

Table 2 Patient characteristics for outcome study (n = 93)

Characters		n
Age, mean (range)	63.4 y (50.4-76.1 y)	93
Presurgery PSA level	28.2 ng/mL (1-248 ng/mL)	93
Extraprostatic extension	73%	67
Seminal vesicle invasion	41%	37
Gleason score		
2-6	22%	20
7	30%	28
8-10	48%	45
Lymph node positive	43%	40
Lymph node density <20%	43%	17
Lymph node density >20%	57%	23
PSA failure	53%	49

meters. A backward selection procedure with a cutoff level of 0.15 was used to choose the most parsimonious model in predicting PSA-free survival. Statistics were performed using SAS (SAS Institute Inc, Cary, NC) and SPSS (SPSS Inc, Chicago, IL) with a significance level of .05.

3. Results

As listed in Table 1, the lowest mean z intensity of PSMA expression was found in benign prostate glands (upper third of core in Fig. 1A), followed by localized prostate adenocarcinoma (positive immunoreactive stained acinar cancer glands in lower two thirds of core in Fig. 1A) and hormone refractory distant metastases, and the highest PSMA expression was observed in the category of regional lymph node metastases (Fig. 1B). As demonstrated in Fig. 2, mean PSMA expression was significantly increased in localized prostate cancer compared with benign prostatic tissue ($P < .001$). The highest level of PSMA expression was observed in hormone-naive regional lymph node metastases, significantly differing from localized prostate cancer, hormone refractory distant metastases, and benign prostatic tissue (all $P < .001$). Interestingly, PSMA expression in hormone refractory distant metastases was comparable with that in localized prostate cancer but was significantly higher than in benign prostatic tissue ($P < .001$). There was no significant difference in the PSMA expression between the patients who had surgery as a monotherapy and the patients
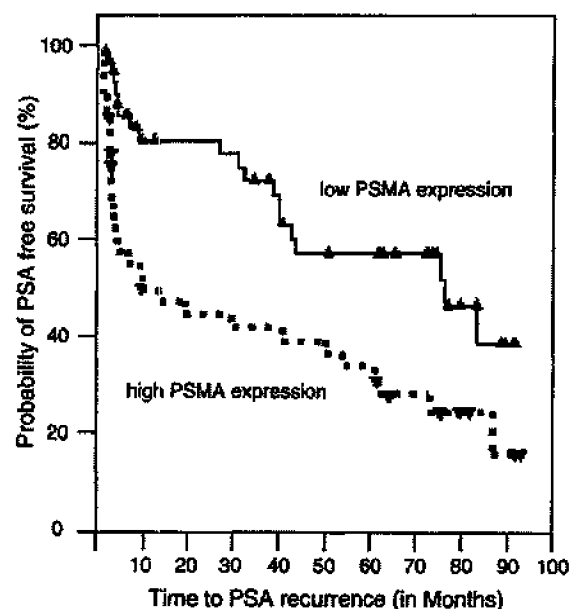
Table 3 Univariate and multivariable Cox regression analysis for outcome study

Univariate analysis	HR	95% CI	P
PSMA expression (>median versus ≤median) (median, −0.35)	2.3	1.3-4.1	.004[a]
Gleason score			
2-6	1	—	—
7	2.1	0.8-5.6	.14[b]
8-10	3.5	1.4-8.6	.006[b]
Extraprostatic extension (yes versus no)	2.7	1.2-6	.017
Seminal vesicle invasion (yes versus no)	3.4	1.9-6.2	<.001
Lymph node			
Negative	1.0	—	—
Density <20%	3.64	1.6-7.9	.001[c]
Density >20%	7.7	3.4-17.3	<.001[c]
Multivariable analysis (adjusted for extraprostatic extension)			
PSMA expression (continuous)	1.4	1.1-2.8	.017
Lymph node positivity	5	2.6-9.7	<.001

[a] High versus low PSMA staining intensity.
[b] Versus GS 2-6.
[c] Versus lymph node negative.

Fig. 3 Kaplan-Meier survival curves for PSMA expression in patients with prostate cancer. Patients with high PSMA-expressing tumors suffered a significant increased rate of PSA recurrent (log rank = 0.003) compared with those patients whose tumors expressed low levels of PSMA.

who received neoadjuvant (preoperative) androgen ablation therapy (data not shown).

Ninety-three patients who had surgery as a monotherapy were included in the outcome analysis. Detailed patient characteristics of the cohort are presented in Table 2. Notably, 40 patients (43%) had lymph node–positive prostate cancer at time of surgery. We divided the cases into 2 groups with high and low PSMA expression defined as positive PSMA stained area above and below the median.

In a univariate Cox regression analysis, high PSMA expression was significantly associated with time to PSA recurrence (HR, 2.3; 95% confidence interval [CI], 1.3-4.1, $P = .004$) (Table 3 and Fig. 3). Other significant predictors of PSA recurrence included Gleason score 8 to 10 (hazard ratio [HR], 3.5; 95% CI, 1.4-8.6, $P = .006$), presence of extraprostatic extension (HR, 2.7; 95% CI, 1.2-6, $P = .017$), and seminal vesicle invasion (HR, 3.4; 95% CI, 1.9-6.2, $P < .001$). High metastatic burden defined as greater than 20% of removed nodes showing metastatic spread was also significantly associated with time to PSA recurrence (HR, 7.7; 95% CI, 3.4-17.3, $P < .001$). In our best multivariable model (Table 3) that included PSMA expression as a continuous variable, lymph node–positive status as well as extraprostatic extension, PSMA expression, and lymph node–positive status stratified according to extraprostatic extension (pT3 stage) were found to be significantly associated with time to PSA recurrence (HR, 1.4; 95% CI, 1.1-1.8, $P = .017$; and HR, 5; 95% CI, 2.6-9.7, $P < .001$, respectively). Stratified according to Gleason score, PSMA expression is not an independent predictor of

PSA recurrence (HR, 1.3; 95% CI, 0.8-1.9; $P = .27$), indicating that PSMA expression and tumor differentiation as determined by the Gleason score may be associated with each other.

4. Discussion

In prostate cancer, Gleason score is still one of the most reliable parameters in predicting progression of disease [14] but, in many studies, fails to predict disease outcome independently [15-17]. Even nomograms using Gleason score in combination with extent of biopsy core involvement, pretreatment serum PSA levels, and clinical stage fail to adequately identify all patients at risk of developing biochemical recurrence [18]. Thus, molecular prognostic biomarkers independently predicting the biologic behavior and outcome of prostate cancer are the focus of many studies [19]. The goal of this study was to characterize immunohistochemical PSMA protein expression in paraffin material as a parameter predicting PSA recurrence in a high-risk patient cohort, applying the new 3E6 monoclonal anti-PSMA antibody on TMAs and using an objective evaluation approach.

In the current study, univariate Cox regression analysis showed that high PSMA expression was significantly associated with PSA recurrence, as were other morphology-driven markers such as high Gleason score, presence of extraprostatic extension, seminal vesicle invasion, and high metastatic tumor burden. At the multivariate level, PSMA overexpression and seminal vesicle invasion were significantly associated with earlier biochemical failure. In concordance with these findings, a previously conducted study in a PSA-screened low-risk cohort of 136 cases could show that high PSMA expressing primary prostate cancers correlated significantly with tumor grade and pathologic stage. Also, patients with high PSMA-expressing tumors suffered a significant increased rate of PSA recurrence compared with those patients whose tumors expressed low levels of PSMA. On the multivariate analysis of that study, pathologic stage and PSMA expression were independent predictors of biochemical recurrence [7]. Both studies demonstrated that overexpression of PSMA in primary prostate cancers is associated with other adverse prognostic factors and independently predicts outcome. Based on the current study results, determining PSMA expression in high-risk cohorts as defined by high PSA levels and advanced prostate cancer may provide additional prognostic information.

As in previous studies, we also found PSMA to be highly overexpressed in prostate carcinoma and prostatic metastases compared with benign prostatic tissue [5-7,20]. In concordance with Bostwick et al [21], we found higher expression of PSMA in high-grade versus low-grade cancers. But contrary to Sweat et al [6], our study demonstrated that the PSMA expression was greater in hormone-naïve

metastases as compared with localized prostate cancer cases. Also, in contrast to Wright et al [22], we did not find PSMA up-regulation in most of the prostate cancer cases after androgen treatment.

Differences in these studies may be due to different antibodies and evaluation of PSMA. Technical protocols for immunoassays are not as standardized and reproducible as McCabe et al [23] recently demonstrated; this can alter outcome results because of different dilutions of antibodies. To avoid subjective evaluation of the PSMA expression within our study, we performed objective evaluation with a semi-automated quantitative approach as described earlier [12,24].

This PSMA expression study on prostate cancer shows that PSMA is expressed to a higher degree in neoplastic prostatic tumors with higher PSMA expression levels predicting adverse outcome not only in a PSA-screened cohort but also in a high-risk non-PSA-screened cohort like ours. One limitation of our survival analysis may be that after excluding patients with neoadjuvant hormone ablation therapy and after excluding patients with hormone ablation therapy before PSA recurrence, our outcome analyses include 93 patients.

Furthermore, these findings on PSMA expression have important implications for disease-specific therapeutic options. PSMA is the prototypical cell-surface marker of prostatic adenocarcinoma (PCa) and therefore provides an excellent target for specific immunotherapeutic options by applying monoclonal antibody conjugates for the management of this malignancy in the stage of progression beyond resectable boundaries [25-27]. Also, PSMA shows promise as a target for diagnostic imaging with antibody radio-conjugates [28,29].

In conclusion, this study of prostate cancer demonstrates that high immunohistochemical PSMA expression in primary tumor independently predicts disease outcome not only in a PSA-screened cohort but also in a high-risk population. Thus, after further validation, immunohistochemical testing for PSMA overexpression has the potential of a clinical test for disease outcome.

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